and crystallized from MeOH-H_2O to yield 2.58 g (56% yield) of 10: mp 155–158°; nmr δ 5.64 (s, -CH=CH-). The mass spectrum showed the molecular ion at m/e 703. *Anal.* ($C_{35}H_{61}NO_{13}$) C, H, N.

Erythronolide A Oxime (11). A solution of 22.55 g (0.032 mol) of 10 in 1.5 l. of 3% HCl in MeOH was left at room temperature for 21 hr. The MeOH was removed *in vacuo*, EtOAc was added to the residue, and the solution was washed with dilute $NaHCO_3$. After drying, the solution was stirred briefly with charcoal, filtered, and concentrated to dryness. Tlc revealed a major spot much slower moving than 10, several minor impurities, and two fast moving spots. Two crystallizations from $(CH_3)_2CO$-C_6H_{14} gave 9.64 g (69% yield) of pure 11: mp 236–239°; ir 1710 cm^{-1} (lactone). The mass spectrum showed the molecular ion at m/e 433. *Anal.* ($C_{21}H_{39}NO_8$) C, H, N.

3,5-Diacetylerythronolide A Acetoxime (12). To 0.300 g (0.69 mmol) of 11 dissolved in 6 ml of anhydrous C_5H_5N was added 1.2 ml (12 mmol) of Ac_2O and the solution was heated at 70° for 16 hr. Solvent was removed using an oil pump, and the residue was dissolved in EtOAc and washed with dilute $NaHCO_3$. After drying, the solution was concentrated *in vacuo* to a solid residue. Crystallization from CH_2Cl_2-Et_2O provided 0.302 g (77% yield) of pure 12: mp 234–235°; nmr δ 2.08, 2.11, and 2.20 (acetyl methyls); $[\alpha]^{25}D$ −51.2° (*c* 0.97, $CHCl_3$). The mass spectrum showed the molecular ion at m/e 559. *Anal.* ($C_{27}H_{45}NO_{11}$) C, H, N.

Erythronolide A (13). To a solution of 0.303 g (0.7 mmol) of 11 in 15 ml of MeOH was added 2.4 g (35 mmol) of $NaNO_2$ in 10 ml of H_2O. After cooling in an ice bath, 35 ml (35 mmol) of 1 *N* HCl was added dropwise with stirring over 15 min. The solution was left at 3° for 5.5 hr and made basic with saturated $NaHCO_3$, and most of the MeOH was removed *in vacuo*. The product was extracted with $CHCl_3$; the extract was dried and concentrated to a foam. Three crystallizations from $(CH_3)_2CO$-C_6H_{14} gave 0.115 g (40% yield) of pure 13: mp 172–173°; ir 1712 (lactone) and 1688 cm^{-1} (ketone); λ_{max}^{EtOH} 290 nm (ϵ 37). The mass spectrum did not give a molecular ion peak but instead gave a peak for $M^+ - 18$ at m/e 400. *Anal.* ($C_{21}H_{38}O_8$) C, H.

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"Hantzsch-Type" Dihydropyridine Hypotensive Agents. 3[1]

Bernard Loev,* Marjorie M. Goodman, Kenneth M. Snader, Ralph Tedeschi, and Edward Macko

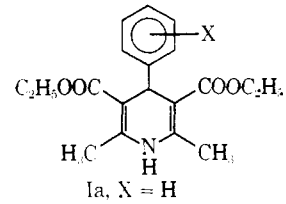
Research & Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received February 22, 1974*

A variety of Hantzsch-type dihydropyridines and related compounds have been prepared in the course of a structure–activity study of these potent hypotensive agents. The biological activity of one of these compounds (Ib) is described. This compound may be exerting its cardiovascular effects through a direct action on vascular smooth muscle. In comparative tests with hydralazine, a clinically used vasodilator, the effects of hydralazine tended to decrease over the treatment period, whereas Ib did not show this same tendency.

The discovery in the 1930's that a dihydropyridine (NADH, a dihydronicotinamide derivative) was a "hydrogen-transferring coenzyme" and consequently of utmost importance in biological systems[2,3] has generated numerous studies of the *biochemical* properties of dihydropyridines. However, there have been relatively few studies of the *pharmacological* activities of such compounds. At the time this work was initiated, the only such reports described weak analgesic and curare-like properties.[4] Consequently, we undertook to evaluate some of these compounds, in particular the "Hantzsch-type" dihydropyridines,[5,6] in a number of standard test systems. Subsequent to our work, antitumor[7] and coronary dilating activities have been reported[8] for certain dihydropyridines.

Early in our studies compound Ia was found to be very potent in producing marked hypotension of long duration (more than 17 min) when administered intravenously to the anesthetized animal. However, it had essentially no activity when administered orally, even at high doses. This paper summarizes the study of structural parameters which was undertaken to determine which features were necessary for activity and which features were necessary for *oral* activity.

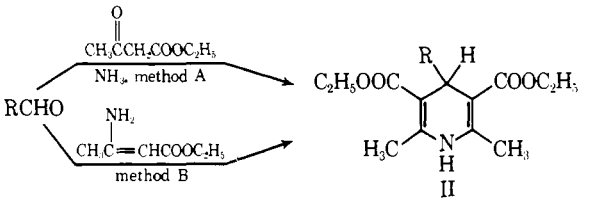
Most of the dihydropyridines (Table I) were prepared



Ia, X = H
b, X = 2-CF3

by a procedure first described by Hantzsch in 1882[9] and which now bears his name; the other compounds were prepared by modified procedures described below. In its most usual form, the Hantzsch reaction involves the simultaneous reaction of an aldehyde, acetoacetic ester, and ammonium hydroxide (Scheme I, method A); it is not necessary—and usually less satisfactory—to isolate the intermediates. The procedure is simple, and isolation of product is generally straightforward. A variation on this procedure, developed by Collie[10] (method B), involves preforming the presumed intermediate aminocrotonic ester and reacting this with the aldehyde under acidic conditions; this method is most useful for the synthesis of 3,5-dicyanodihydropyridines (Table I).

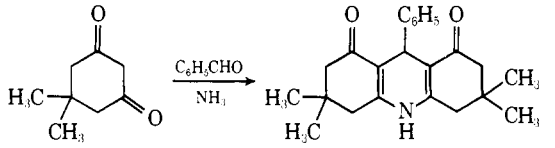
Scheme I



II

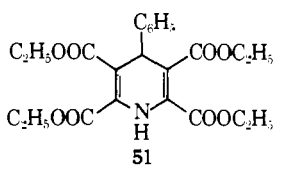
Alkyl, cycloalkyl, cinnamyl, and most aryl aldehydes reacted readily and gave good yields of crude product. However, ortho-substituted benzaldehydes generally gave low yields. Although it had been previously claimed[11] that ortho,ortho'-disubstituted benzaldehydes did not undergo the Hantzsch reaction, we were able to obtain dihydropyridines (although in very low yields) from 2,6-dichlorobenzaldehyde and 2,4,6-trimethylbenzaldehyde (**37** and **38**, Table I).

Compounds in which the 3,5-diester groups are replaced by other electron-withdrawing groups were obtained by replacing the β-keto ester by a variety of β-keto- (or β-amino) nitriles, amides, or ketones (Table I). When the two carbonyl groups of acetoacetic ester were combined into a cyclic structure, *i.e.*, when a cyclic 1,3-diketone was used, the tricyclic dihydropyridine **76** was obtained.†

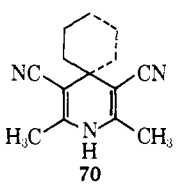


76

When ketomalonic ester was used as the reagent, the new tetraester **51** was obtained. Cyclohexanone reacts to give the spiro compound **70**,‡ unusually stable to hot acids, bases, and oxidizing agents. Neither cyclohexanone nor other ketones undergo the Hantzsch reaction with acetoacetic ester.[14]



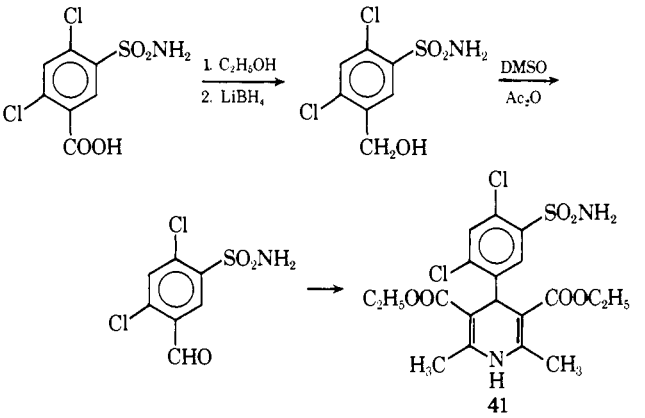
51



70

Two compounds (**40** and **41**) were prepared containing functional groups present in certain diuretics in the hope of combining antihypertensive and diuretic activities into one molecule. Compound **41** was prepared as shown in Scheme II.

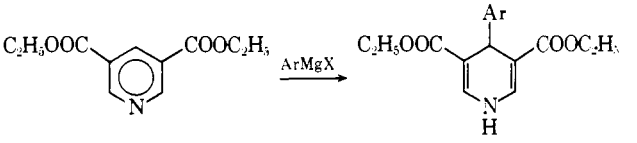
Scheme II



41

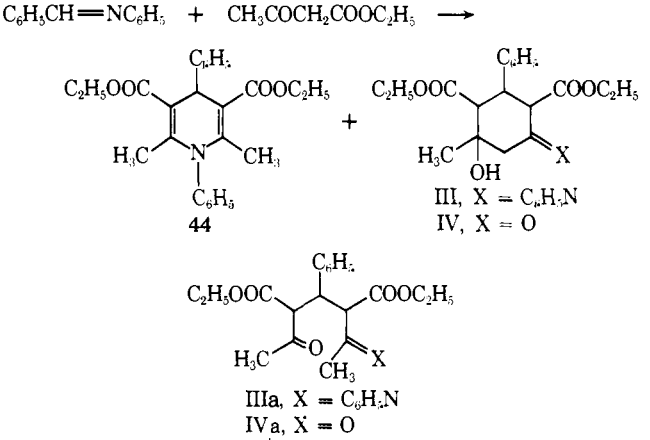
Reaction of aryl Grignard reagents with pyridine-3,4-dicarboxylic ester (Scheme III) gave the 4-aryl-2,6-unsubstituted dihydropyridines (**50** and **52**). Methyl Grignard is reported to give mixtures of 2- and 4-substituted products.[15]

Scheme III



The *N*-phenyldihydropyridine **44** (Scheme IV) has been prepared by reaction of benzalaniline and acetoacetic ester.[16,17] In reproducing this reaction, in addition to the dihydropyridine **44** obtained in small yield, we obtained as the major product another substance III which had previously been assigned the incorrect structure IIIa.[18] This compound was also obtained when the usual Hantzsch conditions were employed. The structure was determined to be III by nmr and by hydrolysis to the keto alcohol IV (which itself has been the subject of a great deal of confusion in the literature[16,19-24] as a result of the original[25] incorrect assignment to it of structure IVa).

Scheme IV

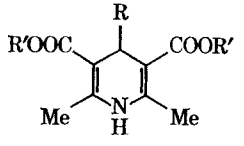


Three *N*-acyldihydropyridines have been reported,[24,26,27] but none of these are of Hantzsch-type compounds II. We have now obtained Hantzsch-type *N*-acyl compounds **43** and **46** by acylation of **21** and **30** using sodium hydride and an acid halide in dimethylformamide.

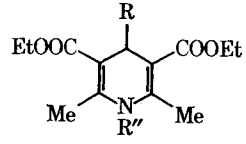
†Goncharova and Dubur[12] have since reported the *N*-carboxymethyl derivative of III without experimental details or physical constants.

‡von Meyer[13] refers to this compound; however, no experimental details or physical constants are given.

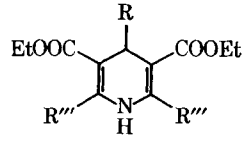
Table I. Chemical and Pharmacological Properties

Compd	R	R′	Hypotensive activity: Dose,[a] mg/kg iv[b] (po[c])	Hypotensive activity: Degree[d]	Hypotensive activity: Duration[e]	Yield, %[f]	Method[g]	Mp or bp (mm), °C	Recrystn solvent[h]	Formula[i]
										
1	H	Et	2.0[j]	+[k]	+	*l*				
2	Me	Et	0.5	+[k]	+	*m*				
3	*i*-Pr	Et	0.5	+	+	61	A	87–97[n]	C	
4	*n*-Hexyl	Et	1.5	+	+	26	A	189–190 (0.1)[o]		$C_{19}H_{31}NO_4$
5	Cyclohexyl	Et	1.5	+++	++	38	A	127–129	C–D	$C_{19}H_{29}NO_4$
6	3-Cyclohexenyl	Et	0.5 (20)	++ (++)	+++ (++)	74	A	139–140	C–E	$C_{19}H_{27}NO_4$
7	3-Cyclohexenyl	*t*-Bu	16.5	++	++	35	A	183–185[p]	F	$C_{23}H_{35}NO_4$
8	Benzyl	Et	6.5	++	+	61	A	115–117[q]	G	
9	Styryl	Et	6.5	+++	+	50	A	148–150[r]	G–H	
10	2-Pyridyl	Et	0.5 (30)	+++ (+++)	+++ (+++)	47	A	192–194[s]	H	
11	3-Pyridyl	Et	0.5 (30)	+++ (NSA)	+++	57	A	189–191[t]	H	
12	4-Pyridyl	Et	1.0 (10)	++ (++)	+++ (+++)	43	A	183–186	I	$C_{18}H_{22}N_2O_4$
13	3-Pyridyl methiodide	Et	16.5	++	+	75		209 dec	J–K	$C_{19}H_{25}N_2O_4 \cdot I$
14	2-Pyrrolyl	Et	0.25 (10)	+++ (+++)	++ (+++)	65	A	216–217	F	$C_{17}H_{22}N_2O_4$
15	2-Thienyl	Et	0.1 (2.5)	+ (+++)	+ (++)	77	A	168–169	H	$C_{17}H_{21}NO_4S$
16	2-Furyl	Me	0.5 (40)	+++ (NSA)	++	47	A	191.5–192.5	H	$C_{15}H_{17}NO_5$
17	2-Furyl	Et	0.5 (5)	++[v] (+++)	+++ (+++)	81	A	165–166[u]	H	$C_{17}H_{21}NO_5$
18	2-Furyl	*t*-Bu	6.6 (40)	+++ (NSA)	+++	59	A	167–169	H	$C_{21}H_{29}NO_5$
19	4-Naphthyl	Et	(80[w])	(NSA)		55	A	195–198[x]	F	$C_{23}H_{25}NO_4$
20	4-Quinolinyl	Et	0.5 (10)	+++ (+++)	+++ (++)	22	A	197.5–200.5[y]	I–L	
21 (Ia)	C_6H_5	Et	0.1[z] (50)	+++[k] (NSA)	+++	50	A	157–159[z]	F	
22	C_6H_5	*t*-Bu	0.5	+[aa]	+	33	A	186–190	C	$C_{23}H_{31}NO_4$
23	2-ClC_6H_4	Et	0.015 (2.5)	++[k] (+++)	++ (+++)	39	A	123–125[bb]	G	
24	2-ClC_6H_4	*t*-Bu	0.5 (40)	++ (NSA)	+++	28	A	191.5–193.5	I–L	$C_{23}H_{30}ClNO_4$
25	2-$CH_3C_6H_4$	Et	0.5 (5)	+++ (+++)	+++ (++)	72	A	104–106[cc]	I–L	$C_{20}H_{25}NO_4$
26	2-$MeOC_6H_4$	Et	0.5 (10)	+++ (+++)	+++ (+++)	15	A	138–143.5[dd]	I–L	$C_{20}H_{25}NO_4$

27	2-MeOOCC$_6$H$_4$	Et	(80[w])	(+++)	(+++)	20	B	137–138	H–N	$C_{21}H_{25}NO_6$
28	2-O$_2$NC$_6$H$_4$	Me	0.01[i]	+++	++	50	A	172–173[oo]	F	
29	2-CF$_3$C$_6$H$_4$	Me	(5)	(+++)	(+++)	40	A	167–169.5	G	$C_{18}H_{18}F_3NO_4$
30 (Ib)	2-CF$_3$C$_6$H$_4$	Et	0.05	+++	+++	24	A	140–142.5	G	$C_{20}H_{22}F_3NO_4$
			(0.315)	(+++)	(+++)	31	B			
			5.0[w]	++	+++					
31	2-CF$_3$C$_6$H$_4$	*t*-Bu	(10)	(+)	(+++)	21	A	156–159	H–N	$C_{24}H_{30}F_3NO_4$
32	3-CF$_3$C$_6$H$_4$	Et	0.05	+++[k]	++	60	A	118–123	G	$C_{20}H_{22}F_3NO_4$
			(5)	(+++)	(+++)					
33	4-CF$_3$C$_6$H$_4$	Et	6.5	+++	++	27	A	121–123	C	$C_{20}H_{22}F_3NO_4$
34	4-HOC$_6$H$_4$	Et	1.2	NSA		64	A	225–229[ff]	H–N	
			(80[w])	(NSA)						
35	4-HOOCC$_6$H$_4$	Et	6.5	+	+++	18	A	229–233	C–I	$C_{20}H_{23}NO_6$
			(40)	(NSA)						
36	4-Me$_2$NC$_6$H$_4$	Et	1.5	++	+	47	A	203 dec[gg]		
37	2,6-Cl$_2$C$_6$H$_3$	Et	0.05	+++[k]	+++	11	A	133–135	I–L	$C_{19}H_{21}Cl_2NO_4$
			(10)	(NSA)						
38	2,4,6-Me$_3$C$_6$H$_2$	Et	0.025	++	+	3.6	A	174–177[hh]	I–L	$C_{22}H_{29}NO_4$
			(40)	(NSA)				162–164		
39	2-Cl-4-HOC$_6$H$_3$	Et	2.8	NSA		25	A	189–193	M	$C_{19}H_{22}ClNO_5$
40	4-Cl-5-H$_2$NSO$_2$C$_6$H$_3$	Et	6.5	+	++	41	A	222.5–224	M	$C_{19}H_{23}ClN_2O_6S$
			(10)	(+)	(+++)					
41	2,4-Cl$_2$-5-H$_2$NSO$_2$C$_6$H$_2$	Et	6.3	++	+++	54	A	270.5–273.5	N–O	$C_{19}H_{22}Cl_2N_2O_6S$
			(20)	(+++)	(+++)					

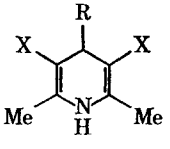
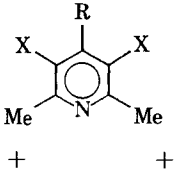


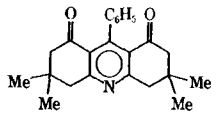
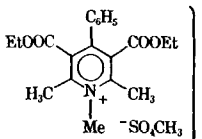
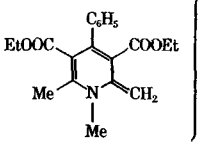
	R	R″								
42	C_6H_5	Me	0.5	+	+	63		130–131[ii]	H	
			(5.0)	(+)	(+++)					
43	C_6H_5	COOEt	(80[w])	(NSA)		42		168–169 (0.1)		$C_{22}H_{27}NO_6$
44	C_6H_5	C_6H_5				1	A	156–158.5[jj]	H	$C_{25}H_{27}NO_4$
45	2-CF$_3$C$_6$H$_4$	Me	1.5	+	++	16	B[kk]	106–109	E	$C_{21}H_{24}F_3NO_4$
			(1.0)	(+)	(+++)					
46	2-CF$_3$C$_6$H$_4$	COOEt	(10)	(+++)	(+++)	44		56–58		$C_{22}H_{26}F_3NO_6$
47	2-CF$_3$C$_6$H$_4$	C_6H_5	(20)	(NSA)		10	A	185–187	M	$C_{26}H_{26}F_3NO_4$



	R	R‴								
48	3-Cyclohexenyl	Et	6.5	+++	+	7	A	113–116	C	$C_{21}H_{31}NO_4$
			(40)	(NSA)						
49	3-Cyclohexenyl[ll]	Benzyl	(16.5)	(NSA)		38	A	Oil		$C_{29}H_{31}NO_4$
50	C_6H_5	H	6.0	+++	+	16		116–117	K	$C_{17}H_{19}NO_4$
51	C_6H_5	COOEt	5.0	+	+	10	A	Oil	C–D	$C_{23}H_{27}NO_8$
52	2-CF$_3$C$_6$H$_4$	H	(80[w])	(+)	(+++)	19		144–146	C–I	$C_{18}H_{18}F_3NO_4$
53	2-CF$_3$C$_6$H$_4$	Et	(5[mm])	(+)	(+++)	13	A	99–104	E	$C_{22}H_{26}F_3NO_4$

Table I (*Continued*)

Compd	R	X	Hypotensive activity: Dose,[a] mg/kg iv[b] (po[c])	Degree[d]	Duration[e]	Yield, %[f]	Method[g]	Mp or bp (mm), °C	Recrystn solvent[h]	Formula[i]
										
54	H	CN	6.5[t]	+	+		*nn*			
55	Me	CN	6.5[t]	+	+++		*nn*			
56	Me	COMe	6.5	+++	+		*m*			
57	*i*-Pr	CN	16.5	+	+	50	B	148–149	D	$C_{12}H_{15}N_3$
58	*t*-Bu	CN	6.5	++	+	38	B	208–210	F	$C_{13}H_{17}N_3$
59	3-Cyclohexenyl	CN				40	B	220–223	H	$C_{15}H_{17}N_3$
60	3-Cyclohexenyl	COMe	6.5 (20)	+++ (NSA)	+++	33	A	159–169	G–P	$C_{17}H_{23}NO_2$
61	3-Cyclohexenyl	CONH-cyclohexyl	16.5	NSA		7	A	129–131	C–I	$C_{27}H_{41}N_3O_2$[oo]
62	3-Cyclohexenyl	CONH-2-pyridyl	6.5	+	+	50	A	218–222	C–Q	$C_{22}H_{27}N_5O_2$[j]
63	3-Cyclohexenyl	CONH-2-pyrimidyl	16.5	NSA		5	A	182 dec	I	$C_{23}H_{25}N_7O_2$[pp]
64	Benzyl	CN	1.5	+	+	20	B	167–170	D	$C_{16}H_{15}N_3$
65	C_6H_5	CN	19.3 (17.5)	+ (+++)	+++ (++)	43	B	208–210[qq]	H	
66	C_6H_5	COMe	0.5	+[k]	+	41	A	180–182[rr]	D–H	
67	C_6H_5	$CONHC_6H_5$	16.5	++	+++	50	A	237–239	R	$C_{27}H_{25}N_3O_2$
68	2-$CF_3C_6H_4$	COMe	0.5 (80[w])	+ (NSA)	+	7	A	187.5–190.5	H–N	$C_{18}H_{18}F_3NO_2$
69	Me, $C_6H_5CH_2$	CN	6.5	+	+	26	B	154–160	H–N	$C_{17}H_{17}N_3$
70	$-(CH_2)_5-$	CN	16	+++	+	30	B	132–133.5	C–I	$C_{14}H_{17}N_3$
										
71	H	COOEt	1.0	+	+	44		72–73[ss]	C	$C_{13}H_{17}NO_4$[j]
72	*i*-Pr	CN	6.5	+++	+	68		82–83 (0.1)		$C_{12}H_{13}N_3$[j]
73	Styryl	COOEt				60		162–165	H–K	$C_{21}H_{23}NO_4 \cdot HCl \cdot 2H_2O$
74	C_6H_5	COOEt	16.5[t]	+	+++	73		63–64.5[tt]	H–N	
75	2-$CF_3C_6H_4$	COOEt	(80[w])	(NSA)		77		71–73[hh]	C	$C_{20}H_{20}F_3NO_2$

	Structure	Miscellaneous							
76	See text	16.5	+	+	24	A	279–280 dec	H–G	$C_{23}H_{27}NO_2$
77					20		258–261	H–G	$C_{23}H_{25}NO_2$[uu]
78		6.5	+++	+	63		143–146[vv]	H–K	$C_{21}H_{27}NO_6S$
79					41		103–104[ww]	H	$C_{20}H_{23}NO_4$

[a]Doses are cumulative. [b]In anesthetized dogs unless otherwise indicated. [c]Data in parentheses are for orally administered compound and in normotensive or neurogenic hypertensive dogs unless otherwise indicated. [d]+++ indicates a blood pressure fall of >50 mm; ++, 40–50 mm; +, 30–39 mm; NSA, no significant activity at indicated dose. [e]In the *anesthetized* animals, +++ indicates a blood pressure lowering lasting >5 min; ++, 3–5 min; +, <3 min. *Orally*, +++ indicates a blood pressure lowering >3 hr; ++, 1–3 hr; +, <1 hr. [f]Based on immediate precursor; yields are after recrystallization. [g]See Experimental Section; method A utilizes a β-keto ester, -nitrile, etc.; method B utilizes β-aminocrotononitrile; where no method is indicated, the synthesis or a typical procedure is given in the Experimental Section. [h]The abbreviations have the following meaning: C, hexane; D, benzene; E, cyclohexane; F, MeOH; G, *i*-Pr_2O; H, EtOH; I, EtOAc; J, $CHCl_3$; K, Et_2O; L, methylcyclohexane; M, MeCN; N, H_2O; O, DMF; P, acetone; Q, *i*-PrOH; R, glyme. [i]In anesthetized cats. [j]All compounds analyzed for C, H, and N and analyzed within ±0.4% of calculated values except for the following compounds. **62,** N: calcd, 16.31; found, 15.71. **71,** C: calcd, 62.20; found, 62.66. **72,** C: calcd, 72.33; found, 71.85. [k]Toxicity observed starting at 1 mg/kg. [l]Kindly provided by Dr. R. Lyle. [m]Purchased from Distillation Products Industries. [n]Lit. mp 97°: F. Engelmann, *Justus Liebigs Ann. Chem.*, **231,** 37 (1885). [o]Lit. mp 54°: A. Jaeckle, *Justus Liebigs Ann. Chem.*, **246,** 32 (1888). [p]Varies markedly depending on rate of heating. [q]Lit.mp 117–118°: A. Jeanrenaud, *Ber.*, **21,** 1783 (1888). [r]Lit. mp 148–149°: W. Epstein, *Justus Liebigs Ann. Chem.*, **231,** 1 (1885). [s]Lit. mp 196–198°: R. F. Homer, *J. Chem. Soc.*, 1574 (1958). [t]Lit. mp 192–194°: R. H. Wiley and J. S. Ridgeway, *J. Org. Chem.*, **26,** 595 (1961). [u]Lit. mp 164°: R. Schiff and J. Puliti, *Ber.*, **16,** 1607 (1883). [v]Toxic at 5 mg/kg. [w]In metacorticoid hypertensive rat.[31] [x]Lit. mp 197.5–198°: H. J. Kahn, V. Petrow, R. L. Rewald, and B. Sturgeon, *J. Chem. Soc.*, 2128 (1949). [y]Lit.[t] mp 203–204°. [z]Lit.[u] mp 156–157°. [aa]Toxic at 2.5 mg/kg. [bb]Lit. mp 132°: L. E. Hinkel and W. R. Madel, *J. Chem. Soc.*, 750 (1929). [cc]Lit. mp 114°: L. E. Hinkel, E. E. Ayling, and W. H. Morgan, *J. Chem. Soc.*, 1835 (1931). [dd]Lit.[bb] mp 151°. [ee]Lit. mp 172–174°: U. S. Patent 3,644,627 (1972); Bayer 1040 (Nifedipine), F. A. Horster, B. Duhm, W. Maul, H. Medenwald, K. Patzschke, and L. A. Wegner, *Arzneim.-Forsch.*, **22,** 330 (1972), and following articles. [ff]Lit. mp 226–227°: B. Emmert, E. Diefenbach, and R. Eck, *Ber.*, **60,** 2216 (1927). [gg]Lit. mp 201°: L. E. Hinkel and H. W. Cramer, *J. Chem. Soc.*, 137 (1920). [hh]Two different melting points observed. [ii]Lit. mp 131°: W. Traber and P. Karrer, *Helv. Chim. Acta*, **41,** 2066 (1958). [jj]Lit.[16] mp 159–160°. [kk]Also prepared by reaction of the sodium salt with MeI (12% yield). [ll]3,5-Dimethyl ester. [mm]In renal hypertensive dog.[33] [nn]Kindly provided by Dr. E. M. Kosower. [oo]C: calcd, 73.76; found, 71.78. [pp]C: calcd, 64.02; found, 62.71. [qq]Lit. mp 205–206°: E. von Meyer, *J. Prakt. Chem.*, **52,** 81 (1895). [rr]Lit. mp 182–183°: A. P. Phillips, *J. Amer. Chem. Soc.*, **73,** 2248 (1941). [ss]Lit. mp 72°: P. Griess and G. Harrow, *Ber.*, **21,** 2740 (1888). [tt]Lit. mp 66°: S. Skraup, *Justus Liebigs Ann. Chem.*, **419,** 1 (1919). [uu]C: calcd, 79.51; found, 77.93. [vv]Literature melting point of methosulfate salt 150–152°: O. Mumm, *Justus Liebigs Ann. Chem.*, **443,** 272 (1925). [ww]Lit.[vv] mp 110–111°; the methide corresponds to the free base of **78.**

The low basicity of the dihydropyridine nitrogen permitted the selective alkylation of the pyridyl nitrogen in the 3-pyridyl isomer to give the quaternary derivative **13.**

Structure–Activity Discussion. Table I summarizes the hypotensive data on dihydropyridines and related compounds. Activity is described in terms of milligram potency of the compound (dose column), magnitude of blood pressure lowering produced at the lowest effective dose (degree column), and length of time that a significant lowering was produced (duration column).

Although even the simple 2,6-dimethyl-3,5-dicarbalkoxy-1,4-dihydropyridines (compounds 1–4) have some hypotensive activity in the anesthetized animal, good activity is generally only observed with those compounds having a cyclic substituent in the 4 position, particularly the 4-aryl compounds. The most active compounds were the 4-heteroaryl and the 4-ortho-substituted phenyl derivatives. Activity usually decreases as the ortho substituent is moved to the meta and even more so when moved to the para position on the phenyl ring. Activity is generally independent of the electronegativity of the substituent on the phenyl ring since compounds possessing both electron-withdrawing (compounds **23** and **27–29**) and -donating (**25** and **26**) substituents in the ortho position of the 4-phenyl group are active. This suggests that activity may be enhanced by the presence of bulky groups which cause the 4-substituent to prefer an orientation perpendicular to the plane of the dihydropyridine ring. This theory is supported by the very high activity shown by the ortho,ortho'-substituted compounds **37** and **38.** Phillips[4] suggested that a similar relationship might exist between steric effects and curare-like activity of the dihydropyridines which he investigated.

Substitution on the nitrogen usually decreases potency (**29** *vs.* **45–47**). Of the substituents studied at the 2,6 position, 2,6-dimethyl substitution is best (**6** *vs.* **48** and **49**). Replacement of the 3,5-carbalkoxy groups by other electron-withdrawing substituents produces a marked decrease in activity but, of these, the 3,6-diacetyl compounds generally were the most active. There is little difference in potency between the methyl and ethyl esters in the anesthetized animals but the ethyl esters usually had greater oral potency; the *tert*-butyl ester was generally less active.

The oxidized (aromatic) compounds were generally of a very low order of activity (**21** and **30** *vs.* **74** and **75**). Good oral activity was most consistently observed among the 4-heteroaryl and 4-ortho-substituted phenyl compounds, but the latter generally showed greater activity and fewer signs of toxicity. Dihydropyridine **41**, which contains some of the structural features of certain diuretics, had only modest hypotensive activity but did produce diuresis in the phosphate–mannitol dog[28] although it was inactive in the saline-loaded rat.[29] This diuretic profile is characteristic of diuretics such as furosemide.§

Ib[&] was selected for further study on the basis of its potency, low toxicity, and general profile of activity.

Pharmacology of Ib. A preliminary description of the cardiovascular activity of Ib (**30**) has appeared.[1] The compound lowers blood pressure in rats, guinea pigs, cats, and dogs; it is active by the intravenous, intragastric, and oral routes of administration and is effective in normotensive animals and in animals with experimental hypertension.

In normotensive anesthetized cats and dogs,[30] Ib produced marked hypotension following intravenous doses ranging from 0.01 to 0.5 mg/kg. In rabbits anesthetized with Dial–urethane. systolic, diastolic, and mean arterial blood pressure was lowered after intravenous doses of 0.05 mg/kg. Guinea pigs intubated with doses of 10 mg/kg of Ib exhibited hypotension averaging 34 mm for as long as 40 min after treatment. Metacorticoid hypertensive rats[31] exhibited hypotension after oral doses of 2.5–10 mg/kg daily for 2–5 days.

Ib was compared with hydralazine in unanesthetized normotensive dogs at doses ranging from 1.25 to 10 mg/kg. Both compounds produced similar degrees of hypotension, and tachycardia was seen during the drug-induced hypotensive phase of each drug. Although the severity of tachycardia produced by the two drugs was initially similar, the hypotensive effects and tachycardia seen with hydralazine tended to disappear over the course of the study. However, Ib continually produced hypotension (accompanied by tachycardia).

In the unanesthetized neurogenic hypertensive dogs[32] there was a good response to the hypotensive effects after oral doses ranging from 1 to 10 mg/kg. At the higher doses hypotension persisted for greater than 24 hr. In renal hypertensive dogs[33] Ib produced significant hypotension accompanied by tachycardia after oral doses of 5 mg/kg.

Experiments carried out in an effort to elucidate the mode of action of this drug in producing hypotension included a study of the effects of Ib on the autonomic pathways—bilateral carotid occlusion (BCO), central vagal stimulation (CVS), peripheral adrenergic mediators, contractions of the cat nictitating membrane—and on the release or depletion of catecholamines. A number of generalizations can be made: Ib reduces the autonomic pressure reflexes of BCO and CVS; it does not appear to be a ganglionic blocker nor does it act on cholinergic sites; it has some β-adrenergic inhibition and may produce weak α-adrenergic inhibition. However, it does not block the effect of epinephrine on contraction of the nictitating membrane.

Release or depletion of catecholamines does not provide an adequate explanation for the observed hypotensive potency of Ib. The data are compatible with the hypothesis that Ib is acting by direct vascular relaxation. Spiral strips of canine artery[34] were relaxed by small doses of the drug. Hemodynamic effects measured in unanesthetized dogs showed that contractility was diminished as blood pressure fell but returned to previous levels long before the pressure returned.

The compound has no effect on glomerular filtration rate[35] and produces a slight decrease in plasma potassium when tested in renal clearance studies, but otherwise does not influence urine output on diuretic testing in rats.[29] It produced some increase in blood sugar in guinea pigs and rats.[36] It should be noted that these effects occurred at high doses of 100 mg/kg orally.

Ib did not alter the urinary excretion patterns of either porphobilinogen or *d*-aminolevulinic acid[37] and is not implicated with porphyria.[38] The compound does not have an effect on gastric motility or secretion[39] of rats.

With respect to CNS activity, Ib produced some indication of weak tranquilizing or depressant action. It has an ED_{50} of 97 (36–204) mg/kg orally for the protection of mice against the effects of maximal electroshock[40] but is only slightly active in raising the minimal electroshock threshold in mice and in rats. Ib had no analgesic activity, failing to elevate the pain threshold[41] after all doses as high as 200 mg/kg. Its oral ED_{50} in suppressing rage in fighting mice is 56 (44–72) mg/kg.

The compound is relatively nontoxic when administered orally to mice and rats. In mice the acute LD_{50} is 1480 (1276–1717) mg/kg, and in rats the LD_{50} is 1225 (811–1850) mg/kg. Intravenously, a lethal effect was produced

§Lasix.
&SKF 24260.

in rats after 5 or 10 mg/kg, whereas a dog expired after receiving 0.7 mg/kg intravenously.

The compound has been tested in seven patients with moderate essential hypertension, and blood pressure lowering was observed beginning at an oral dose of 5–7 mg.[42] Further clinical studies are in progress.

Experimental Section**

Pharmacology. The cardiovascular activity of these compounds, after intravenous administration, was determined in ether-chloralose anesthetized cats. Blood pressure was recorded *via* a Sanborn pressure transducer and recorder. Blood pressure responses to standard autonomic challenges (epinephrine, dimethylphenylpiperazinium, furfuryltrimethylammonium iodide, histamine, peripheral vagal stimulation, and bilateral carotid occlusion) are determined prior to administration of the test drug. The drug is then given iv and the effect on resting arterial blood pressure is recorded, as well as the effect on the responses to the autonomic challenges.[30]

For oral activity, the compounds were evaluated in unanesthetized neurogenic hypertensive dogs.[32] The control mean blood pressure (MBP) and its 95% confidence limits of each trained dog were determined from six readings over a period of several weeks prior to dosing. The test compounds were generally dosed at 1, 2.5, 5, and 10 mg/kg to two or three dogs on 2 consecutive days. The systolic and diastolic blood pressures were determined after dosing and were converted to MBP's. The MBP's thus obtained were compared with the control MBP's of the same dog. The statistical method for calculation of confidence limits is based on a modification of the *t* test.[43]

In a few instances, the compounds were tested for oral activity in metacorticoid rats.[31] The systolic and diastolic blood pressures were measured before and after (5 and 24 hr) oral administration of the compounds; the mean arterial blood pressures were then calculated and evaluated.

Synthesis of Dihydropyridines. The procedures given below are representative for the variously substituted dihydropyridines prepared by "Hantzsch" procedures using either ethyl acetoacetate (method A) or β-aminocrotonitrile (method B).

Method A. 4-(2-Trifluoromethylphenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (Ib, 30). *o*-Trifluoromethylbenzaldehyde acetal (PCR, Inc.) (12 g, 0.0485 mol) was mixed with 50 ml of 6 *N* HCl and the mixture was refluxed in an N_2 atmosphere for 3 hr. The solution was then cooled and poured into a separatory funnel. The bottom green oil was separated and the aqueous layer washed with 25 ml of CH_2Cl_2. The combined oil and extract were placed in a round-bottomed flask and to this was added 12.6 g (0.097 mol) of ethyl acetoacetate, followed by 25 ml of ethanol and 5 ml of concentrated NH_4OH. The yellow mixture was refluxed overnight, then chilled, and poured onto 500 ml of ice water. An oil separated and slowly formed a gum which crystallized from *i*-Pr_2O to give 4.6 g (24% yield) of white product.

Method B. 4-(*tert*-Butyl)-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine (58). A mixture of 32.8 g (0.4 mol) of β-aminocrotonitrile, 17.2 g (0.2 mol) of pivaldehyde, and 100 ml of glacial AcOH was heated at reflux temperature overnight and chilled, and the solid which separated was filtered and washed with Et_2O. Recrystallization from MeOH gave 16.4 g (38% yield) of product.

4-(2,6-Dichlorophenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (37). The reaction was run as in method A, using 17.5 g (0.1 mol) of 2,6-dichlorobenzaldehyde, 26 g (0.2 mol) of ethyl acetoacetate, and 10 ml (0.15 mol) of concentrated NH_4OH. After refluxing overnight the solution was poured into ice water and the oil which separated was extracted into CH_2Cl_2; the extract was dried ($MgSO_4$) and concentrated to give an orange oil. The oil was partially crystallized by washing with hot hexane and then decanted from the crystals. The crystals were pressed on a porous plate to dry and then recrystallized from methylcyclohexane–ethyl acetate to give 4.4 g (11% yield) of product.

4-(2,4,6-Trimethylphenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (38). To a solution of 20 g (0.135 mol) of mesitaldehyde in 80 ml of ethanol was added 35.1 g (0.27 mol) of ethyl acetoacetate followed by 13.5 ml (0.2 mol) of concentrated NH_4OH. The mixture was heated at reflux temperature for 6 hr and then poured into ice water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), concentrated on the steam bath, and then heated *in vacuo* at 0.35 mm to remove fractions which boiled to 142°. The pot residue was slurried with hexane to give a solid which was recrystallized from methylcyclohexane containing a little ethyl acetate to give 0.8 g (1.6% yield) of product.

4-(2,4-Dichloro-5-sulfamylphenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (41). To 58 kg (498 mol) of chlorosulfonic acid was added, with stirring, 17.7 kg (92.6 ml) of 2,4-dichlorobenzoic acid (Tenneco) over a 10-min period. The mixture was then heated to 140–145° for 2 hr, cooled to 105°, and stirred overnight while cooling to room temperature. The reaction was quenched by the addition of 285 kg of ice over a 4-hr period, and the solid was then filtered, washed with H_2O, and air-dried giving 23.4 kg of 2,4-dichloro-5-chlorosulfonylbenzoic acid: mp 183–185° (from C_6H_5); 88% yield.

The sulfonyl chloride (14 kg, 30.9 ml) was added to 45 ml of concentrated NH_4OH over a period of 25 min at 0–10° with good stirring. The mixture was stirred for 1.5 hr at −10°, diluted with ice, and acidified with concentrated HCl. The resulting solid was filtered, washed with water, and recrystallized from MeOH–H_2O to give a 76% yield of sulfonamide, mp 223–226°. *Anal.* ($C_7H_5Cl_2NO_4S$) C, H, N.

A solution of 74 g (0.28 mol) of the sulfonamide in 1.5 l. of ethanol was stirred well as HCl gas was bubbled through it for 2 hr. The temperature of the solution was controlled by occasional cooling in ice. The solution was then refluxed for 2 hr and concentrated to dryness. The resulting solid ester (73 g), mp 108–113°, was recrystallized from *i*-PrOH: mp 113–116°.

To a solution of 73 g (0.24 mol) of the ester in 300 ml of dry THF was added dropwise, with stirring, 19.6 g (0.9 mol) of $LiBH_4$ in 150 ml of THF. The mixture was stirred and refluxed for 5 hr, then left at room temperature for 60 hr, and was then *carefully* diluted with 300 ml of H_2O. The mixture was filtered from a gray lumpy solid and the filtrate was concentrated to remove the THF. On chilling, a white solid separated and was collected, dissolved in a solution of 500 ml of hot H_2O and 100 ml of *i*-PrOH, charcoaled, and acidified with concentrated HCl to pH 2. The white solid alcohol separated and was collected: mp 195.5–201°; 36 g (58% yield). Recrystallization from *i*-PrOH gave mp 201–204.5°. *Anal.* ($C_7H_7Cl_2NO_3S$) C, H, N.

To a solution of 33 g (0.13 mol) of the alcohol in 390 ml of dry DMSO was added 260 ml of acetic anhydride. After 22 hr the solution was poured into ice–H_2O (800 ml) with stirring and an oil separated which slowly crystallized. The solid was collected and recrystallized from H_2O–*i*-PrOH (1:1) to give 12.5 g of solid, mp 200–203°. The solid was heated with stirring with 200 ml of 3 *N* HCl for 5 min. The solid dissolved and then white needles separated. After cooling the solid aldehyde was collected: 9.7 g; mp 168–170°; 29% yield. Recrystallization from H_2O–*i*-PrOH gave mp 170–172°. *Anal.* ($C_7H_5Cl_2NO_3S$) C, H, N.

To a solution of 6 g (0.024 ml) of the aldehyde in 50 ml of EtOH was added 6.24 g (0.048 mol) of acetoacetic ester and 2.1 ml of concentrated NH_4OH, and the mixture was then refluxed for 3 hr. A white solid separated during refluxing. The mixture was cooled and filtered, and the solid washed with cold EtOH and then recrystallized from DMF–H_2O to give 6.2 g (54% yield) of 41.

4-Phenyl-2,3,5,6-tetracarbethoxy-1,4-dihydropyridine (51). To a solution of 28.3 g (0.15 mol) of diethyl oxalacetate in 7.97 g (0.75 mol) of benzaldehyde and 20 ml of EtOH was added 10 ml (0.15 mol) of concentrated NH_4OH. The mixture was heated at reflux temperature for 20 hr. After cooling, the mixture was filtered and the filtrate poured into water; the oil which separated was extracted into Et_2O; the ethereal layer was washed, dried, and evaporated to give an oil which was further purified by "dry-column" chromatography[44] on alumina, using methylene chloride. The first fraction was concentrated to give an oil which precipitated from benzene–petroleum ether to give 3.5 g of 51.

4,4-Pentamethyleneyl-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine (70). To 42 g (0.51 mol) of β-aminocrotononitrile dissolved in 125 ml of glacial HOAc was added 25 g (0.255 mol) of cyclohexanone. After heating at reflux temperature for 2 hr, the solution was cooled and poured into 500 ml of H_2O and an oil separated. The aqueous layer was decanted, fresh water added, and the oil crystallized. The latter was filtered and recrystallized from EtOAc–hexane to give 70, 17.3 g.

**Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline & French Laboratories and where analyses are indicated by the symbols of the elements, analytical results for the elements were within ±0.4% of the theoretical values. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN 6E spectrometer. Nmr spectra were obtained on a Varian T-60 instrument (Me_4Si). Ir and nmr spectra of all compounds were consistent with the assigned structures.

3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (76). To a mixture of 28 g (0.2 mol) of methone, 10.6 g (0.1 mol) of benzaldehyde, and 75 ml of ethanol was added 10 ml (0.15 mol) of concentrated ammonium hydroxide. The solution was heated at reflux temperature for 2 hr, left at room temperature overnight, and then poured into 500 ml of water. The solid which separated was collected and recrystallized from EtOH–*i*-Pr_2O to give 8.4 g (24% yield) of **76**.

4-(3′-Pyridyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine *N*′-Methiodide (13). A solution of 0.6 mol of the dihydropyridine 11 in 50 ml of $CHCl_3$ was treated with 10 ml (0.6 mol) of methyl iodide. The solution was heated at reflux temperature for 2 hr, allowed to stand overnight at room temperature, and concentrated to give a semisolid. This was dissolved in a small amount of $CHCl_3$ by warming, and Et_2O was added slowly to give a yellow solid which was filtered and recrystallized from $CHCl_3$–Et_2O to give 3.7 g (75% yield) of product.

***N*-Carbethoxy-1,4-dihydropyridines.** A solution of 10 g (0.03 mol) of 2,6-dimethyl-3,5-dicarbethoxy-4-phenyl-1,4-dihydropyridine (**21**) in THF was added dropwise to a stirred suspension of 1.4 g (0.0334 mol) of sodium hydride (57% dispersion in mineral oil) in 150 ml of THF. When addition was complete, the mixture was heated at reflux for 15 min and cooled to room temperature, and then sufficient DMF was added to dissolve the precipitate. To this solution was added, dropwise, 3.62 g (0.0334 mol) of ethyl chloroformate. The mixture was stirred at room temperature for 15 min and then heated at reflux for 18 hr. The mixture was cooled and filtered and the filtrate concentrated. The resulting oil was dissolved in 75 ml of MeCN, washed twice with 70 ml of hexane, and concentrated. The residue was stirred with hexane and 3 g of insoluble unchanged starting pyridine filtered; the filtrate was evaporated to give 7.3 g of crude oil. Purification by "dry-column" chromatography[44] on alumina, using methylene chloride, gave 5 g (42% yield) of 2,6-dimethyl-1,3,5-tricarbethoxy-4-phenyl-1,4-dihydropyridine (**43**) as a colorless oil.

In the same way, 2,6-dimethyl-1,3,5-tricarbethoxy-4-(2′-trifluoromethylphenyl)-1,4-dihydropyridine (**46**) was prepared in 44% yield.

***N*-Methyl-4-(2-trifluoromethylphenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (45). A. By N-Alkylation of Dihydropyridine.** To a suspension of 3.02 g (0.072 mol of 57% dispersion in mineral oil) of NaH in DMSO was added dropwise with stirring 5 g (0.026 mol) of dihydropyridine **30**. The reaction mixture was warmed to 50° while stirring until H_2 evolution ceased (about 1 hr) and most of the solid dissolved. The mixture was cooled to room temperature and 35 ml (0.55 mol) of MeI was added dropwise, with cooling. The solution was stirred at 25° for 18 hr, poured on ice, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and concentrated to give an oil which was taken up in CH_3CN and filtered to remove mineral oil. The filtrate was concentrated to give 3 g of oil which crystallized from EtOH–H_2O. It was recrystallized several times from cyclohexane to give 0.65 g (12% yield) of **45**. Compound **42** was prepared in a similar fashion from **21**.

B. From β-Methylaminocrotonate. To 14.8 g (0.103 mol) of ethyl β-methylaminocrotonate in 40 ml of glacial HOAc was added 10 g of *o*-trifluoromethylbenzaldehyde. The solution was stirred and heated on a steam bath for 0.5 hr and then poured into ice water and an orange oil separated. The H_2O was decanted and the oil was taken up in CH_2Cl_2, washed with H_2O, dried, and concentrated to give an oil which solidified on stirring with hexane to give 3.4 g (16% yield) of **45**.

1,4-Diphenyl-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (44). A mixture of 10.6 g (0.1 mol) of benzaldehyde, 9.3 g (0.1 mol) of aniline, and 26 g (0.2 mol) of acetoacetic ester was heated on the steam bath for 10 hr. The resulting oil was dissolved in EtOH and then poured into ice–H_2O. The oil that separated was extracted with Et_2O, and the solution was dried ($MgSO_4$) and concentrated; the residue slowly formed a semisolid. The semisolid was stirred with cyclohexane and the white insoluble material was filtered: 19 g; mp 90–125°. The filtrate on removal of solvent left 23 g of oil (A) which consisted mostly of III. It was further examined as described later.

The solid was recrystallized from *i*-Pr_2O. The material that crystallized was mostly additional III. The filtrate on concentration to a small volume deposited 1.7 g of a pale yellow solid, mp 100–133°; further concentration of this filtrate gave an additional 1.7 g of III. The yellow solid was recrystallized twice from EtOH giving 0.6 g of **44**, mp 156–158.5° (lit.[16] mp 159–160°). *Anal.* ($C_{25}H_{26}NO_4$) C, H, N. When the reaction was carried out using 0.1 mol of preformed benzalaniline and 0.2 mol of acetoacetic ester, the same work-up procedure was employed and the same mixture of products was obtained.

The α-trifluoromethyl analog **47** was prepared in the same manner from α-trifluoromethylbenzaldehyde, aniline, and acetoacetic ester.

5-Methyl-3-phenyl-5-hydroxy-2,4-dicarbethoxycyclohexanone Anil (III). The 23 g of oil A from the above reaction crystallized on standing. It was triturated with *i*-Pr_2O, and the insoluble material, 3.4 g, was filtered: mp 100–135°. After several recrystallizations from EtOH it melted at 150–151.5°. *Anal.* ($C_{25}H_{29}NO_5$) C, H, N. Hantzsch[25] incorrectly assigned structure IIIa to this compound and reports mp 150°. Additional quantities (4 g) of III were obtained from the various filtrates described under compound **44** (above). The same product was obtained, in approximately equal amounts, from the benzalaniline reaction referred to above. III shows: ir (Nujol) 2.8 (sharp, unassociated OH), 5.8 (sharp, ester), 6.1 (sharp, C=N), 6–7 μ (multiplets, phenyl absorption); nmr ($CDCl_3$) shows a single CH_3 appearing as a *singlet* at 1.25 ppm (structure IIIa would have shown another CH_3 further downfield) and an exchangeable proton at 3.7 ppm (OH).

5-Methyl-3-phenyl-5-hydroxy-2,4-dicarbethoxycyclohexanone (IV). A mixture of benzaldehyde (10.6 g, 0.1 mol), acetoacetic ester (26 g, 0.2 mol), and 2 ml of piperidine in 5 ml of EtOH slowly deposited yellow crystals on standing at room temperature. After 18 hr the solid was filtered and recrystallized from EtOH to give 20.5 g of IV, mp 155–158°. *Anal.* ($C_{19}H_{24}O_6$) C, H, N. This compound, mp 156–157°, has previously been reported but, with one exception,[22] assigned incorrect structure IVa.[16,19,20,21,23,24]

IV was recovered unchanged after heating with concentrated NH_4OH in EtOH for 2 hr. It would have been expected to have been converted to **44** if it had structure IVa. For IV: ir (Nujol) 2.8 (sharp, strong, unassociated OH), 5.75 (sharp, ketone), 5.83 μ (sharp, ester); nmr ($CDCl_3$) shows a *single* CH_3 appearing as a singlet at 1.3 ppm (structure IVa would have shown another CH_3 further downfield); addition of deuterium oxide resulted in complete loss of the hydroxyl peak at 3.7 ppm.

A sample of III was heated for 15 min with dilute HCl. On cooling, a solid crystallized which proved to be identical, by ir and melting point, with IV prepared above.

4-Phenyl-3,5-dicarbethoxy-1,4-dihydropyridine (50). To an ethereal solution of 4.2 g (0.019 mol) of 3,5-dicarbethoxypyridine in Et_2O at −10° and under an N_2 atmosphere was added an ethereal solution containing 0.15 g of CuCl and then 63 ml (0.019 mol) of a 3 *M* ethereal phenylmagnesium bromide solution. After 30 min a saturated aqueous NH_4Cl solution was added. The ethereal layer was dried ($MgSO_4$) and concentrated to give 8.5 g of yellow oil which was purified by "dry-column" chromatography[44] on a 5 × 80 cm silica gel column using Et_2O. The product was obtained as a solid: 3.7 g; mp 117–118° (from ether).

4-(2-Trifluoromethylphenyl)-3,5-dicarbethoxy-1,4-dihydropyridine (52). To a mixture of 0.5 g (0.22 mol) of magnesium in 100 ml of Et_2O was added 5 g (0.022 mol) of *o*-bromobenzyltrifluoride. After standing at 25° for 2.5 hr under N_2, a solution of 4.9 g (0.022 mol) of 3,5-dicarbethoxypyridine in an equal volume of Et_2O was added. The mixture was stirred at 25° for 18 hr, heated at reflux temperature for 1 hr, and then quenched with cooling by dropwise addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O; the extract washed with H_2O and saturated aqueous NaCl, dried, and concentrated to an oil. The oil was purified by "dry-column" chromatography[44] on silica gel and developed with Et_2O to give a solid which on recrystallization from EtOAc–hexane gave 1.5 g (19% yield) of **52**.

Typical Oxidation. 4-(2-Trifluoromethylphenyl)-3,5-dicarbethoxy-2,6-dimethylpyridine (75). To a warm solution of 35 g (0.088 mol) of dihydropyridine **30** in 350 ml of glacial HOAc was added, with vigorous stirring, 35 g (0.51 mol) of sodium nitrate. The solution spontaneously heated to reflux; after reflux subsided, the solution was heated on the steam bath for 20 min, cooled, and poured into ice–H_2O. The solid that separated was filtered and crystallized from EtOH–H_2O to give 27 g (77% yield) of **75**.

***N*-Methyl-4-phenyl-2,6-dimethyl-3,5-dicarbethoxypyridinium Methosulfate (78).** To 9 g (0.0277 ml) of pyridine **74** was added 2.9 ml (0.0304 mol) of methyl sulfate. The mixture was stirred and heated to 65–75° overnight. After cooling, the solid crystal mass was triturated with Et_2O and filtered, and the solid recrystallized from EtOH–Et_2O to give 7.9 g (63% yield) of **78**.

Methide of Compound 78 (79). The above methosulfate salt **78** was dissolved in 100 ml of H_2O and an excess of 10% NaOH was added. A solid formed which was filtered, washed with water, and triturated with a small amount of EtOH to give 3.3 g (41% yield) of **79**, mp 103–104°.

The methosulfate of compound **75** was prepared and converted to the methide in the same manner to give a solid melting at 89–91°. The latter was unstable and decomposed on standing 1 week.

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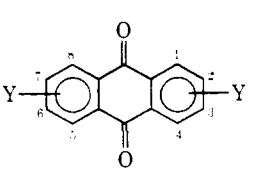
Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1,2] 5. Bis-Basic Ethers of Anthraquinone and Bisalkamine Esters of Anthraquinonedicarboxylic Acids

Arthur D. Sill,* Edwin R. Andrews, F. William Sweet, Jake W. Hoffman, Paul L. Tiernan, J. Martin Grisar, Robert W. Fleming, and Gerald D. Mayer

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215. *Received March 22, 1974*

2,6-Bis[2-(diethylamino)ethoxy]-9,10-anthracenedione dihydrochloride (**10**, RMI 10,024DA) was found to prolong survival of mice infected with lethal challenges of encephalomyocarditis (EMC) virus. It was effective by oral as well as subcutaneous administration and showed broad spectrum antiviral activity. It was selected for preclinical evaluation from a series of congeners that were synthesized to determine structure–activity correlations. These indicated that the 2,6- and 2,7-position isomers showed much greater activity than the 1,4, 1,5, or 1,8 isomers and that elongation of the side chains and increase of molecular weight of the dialkylamine substituent led to decreased oral activity. The congeners **5**, **6**, 11, and 15 also showed high antiviral activity. Bis(3-dibutylaminopropyl) 9,10-dihydro-9,10-dioxoanthracene-2,6-dicarboxylate dihydrochloride (**4**) and 9,10-dibutylidene-2,6-bis[2-(diethylamino)ethoxy]-9,10-dihydroanthracene dihydrochloride (**26**) showed antiviral activity on subcutaneous administration.

The preceding paper of this series[2] described the synthesis and biological evaluation of the anthraquinonesulfonamides I. Earlier, the antiviral activity of several fluorenone derivatives,[2–5] including tilorone hydrochloride,[4,6,7] was reported from our laboratories. Since these included bis-basic esters[3] and ethers,[4] the synthesis of the corresponding anthraquinone derivatives II and III was undertaken.



I, Y = $-SO_2NH(CH_2)_nNR_2$
II, Y = $-CO_2(CH_2)_nNR_2$
III, Y = $-O(CH_2)_nNR_2$

Chemistry. The bisalkamine esters of 9,10-dihydro-9,10-dioxoanthracene-1,5-, 1,8-, and 2,6-dicarboxylic acid